Docket Number: 50623.00266



In Re Application Of:

Examiner:

Sheeba Ahmed

Stephen Dirk Pacetti

Art Unit:

1773

Serial No: 10/606,711

Filed:

June 26, 2003

For:

COATINGS FOR IMPLANTABLE

MEDICAL DEVICES

COMPRISING HYDROPHOBIC AND HYDROPHILIC POLYMERS

DECLARATION UNDER 37 CFR § 1.131

- I, Stephen D. Pacetti, declare as follows:
- The application identified above was filed on June 26, 2003. 1.
- I conceived of or invented the subject matter of the application identified above in the 2. United States prior to February 23, 2003. See Appendix A – redacted invention disclosure form.
- I provided this invention disclosure form to our patent attorneys, through the manage-3. ment of Advanced Cardiovascular Systems, Inc., the assignee of this patent application on April October 9, 2002. Advanced Cardiovascular Systems, Inc. approved the invention for filing a patent application. Our patent attorneys filed the application on June 26, 2003.
- I further declare that all statements made herein of our own knowledge are true and that 4. all statements made upon information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

Docket Number: 50623.00266

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed at San Jose, California on this 6th day of July, 2006.

By: Styler acett
Stephen D. Pacetti

APPENDIX A

For Legal Department Use Only

Docket No.: 3800

Date Assigned: 10/10/02

Date Discl. Rec'd: OCT 0 9 2002

Drug Velwing

INVENTION DISCLOSURE FORM

ADVANCED CARDIOVASCULAR SYSTEMS, INC.

This is a form for disclosing ideas and inventions to the Guidant Legal Department for patent consideration. This form may be used before experimental work has been done. While some of the requested information may not be available at this time, include as much information as you can about the invention. Attach additional sheets if necessary, and sign and date each sheet. Additional information will be requested later.

Please complete each indicated area and return to Intellectual Property Paralegal, Guidant Vascular Intervention Group, 3200 Lakeside Drive, Santa Clara, CA 95052, and a copy to the R&D Director.

1. DESCRIPTIVE TITLE OF THE INVENTION:

Non-Fouling and Protective Coatings for Implantable Medical Devices

Inventors initials: 1 2 2 3

INTRODUCTION

A current paradigm in biomaterials research is the control of protein adsorption on the implant surface. Uncontrolled protein adsorption, leading to mixed layer of partially denatured proteins, is a hallmark of current biomaterials when implanted. Such a surface presents different cell binding sites from adsorbed plasma proteins such as fibrinogen and immunogloblulin G. Platelets and inflammatory cells such as monocyte/macrophages and neutrophils adhere to these surfaces. When so activated, they secret a wide variety of proinflammatory and proliferative factors including PDGF, TNF-α, IL-1β, IL-6, IL-8, IL-10, and TGF-β.

These initial protein adhesion events set the stage for thrombosis and the foreign body response. Several strategies have been put forth to try to mitigate these undesirable surface adhesion events. One approach is to mimic the cell membrane of, for example, endothelial cells. This requires providing the surface with some sort of lipid-bilayer, decorated with glycosaminoglycans, and cellular binding proteins or peptides such as integrins. This has proved to be a complex problem. A simpler strategy is to simply make to surface "stealthy" so that it does not adsorb any proteins. Another name for this type of surface is "non-fouling". If no proteins adsorb, it is known that cellular adhesion and activation is reduced.

Many non-fouling substances have been utilized including poly(ethylene glycol) (PEG), poly(ethylene oxide), hyaluronic acid, dextran, dextrin, dextran sulfate, and heparin. These materials are water-soluble and when cross-linked, or surface immobilized, they form a hydrogel layer on the implant surface. To a first approximation, this hydrogel layer resist protein adhesion by virtue of its extremely low hydrogel/water interfacial tension. There is no thermodynamic driving force for proteins to occupy this interface. Additionally, these materials resist fouling due to their lack of positive charge and water binding properties. For molecules such as PEG, the parameters of surface packing density, and chain length, are known that resist protein adsorption.

The leading configuration for drug eluting stents is a polymer coating on a metal stent. The polymer acts as a reservoir for the drug and, if necessary, can control the drug release rate. Adding a non-fouling surface to a polymer coated drug eluting stent is desirable as it should improve hemocompatibility and mitigate the foreign body response. There are several approaches to adding a surface of PEG or hyaluronic acid to a stent coating. Many of them require grafting with radiation or crosslinking with UV radiation. It is not clear if the drug would be adversely affected by exposure to high levels of gamma radiation or UV. Other approaches require soaking the stent in baths that place the coating on the surface. Immersion of DES stents into baths of water or, more particularly, organic solvents will result in drug leaching into the bath.

Blending PEG, hyaluronic acid, or other non-fouling molecule into the stent coating polymer, and then spraying it on as a topcoat is an attractive choice. It is simple and uses existing technology. Issues include the compatibility of the additive with the coating polymer, mechanical properties of the blend, leaching of the additive into tissue or blood, and whether the additive is actually surface active. For example, optical microscopy studies have indicated that 10% PEG 20K by weight appears to be miscible with EVAL, but at a 25% loading, the PEG phase separates. Phase separated PEG will weaken the EVAL and should leach from the polymer readily. In addition, crude contact angle studies have indicated that PEG blended with EVAL at a 10% loading is not necessarily available at the coating surface after baking. In the attached report, contact angle measurements without any prehydration show 10/90 PEG/EVAL to not that different from pure EVAL.

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Another issue with polymer coated stents, is one of surface contamination during manufacturing. Unlike a metal surfaces, polymer surfaces can be tacky, particularly right after coating. A variety of debris has been observed adhering to DES stents after manufacturing. We have to ubiquitous white fibers, the fairly common blue fibers, and various specks and blobs of contamination. Semisolid and liquid contamination in the form of silicones, oils, and skin oils are also a possibility. The consequences of surface contamination on stents are well known and include inflammation, granuloma formation, and greater neointimal formation. The 3 month Wayne implant demonstrated some granuloma in the control and coated arm.

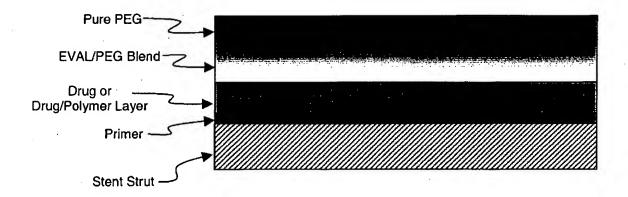
DISCLOSURE

(a) What is disclosed is a polymer coated, drug eluting stent that has the following two outermost layers:

Topmost Layer: This layer consists of a water soluble, biocompatible polymer, which is intended to protect the underlying layer, dissolve in vivo, and be compatible with a hydrophilic additive in the underlying layer

Underlying Layer: This layer is intended to be permanent and consists of a blend of a structural polymer, such as EVAL, and a non-fouling, hydrophilic additive, such as PEG. This underlying layer can be a "topcoat" for controlling drug release, or it may be exist only to present a non-fouling surface to the in-vivo environment after the topmost layer has dissolved.

A schematic of this coating configuration is shown below. In this diagram, the topmost layer is of PEG. The underlying layer is a blend of PEG with EVAL.



The gradient in color between the topmost layer and underlying layer is intended to indicate a gradient of PEG concentration. The pure PEG of the topmost layer should induce an enrichment of PEG at the interface between the two layers.

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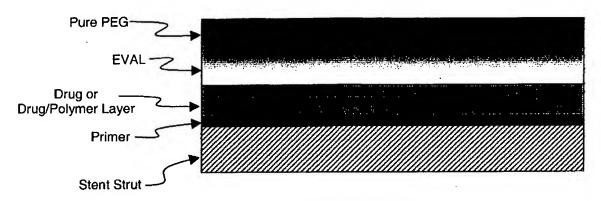
In studies so far, blending PEG with EVAL did not necessarily assure a large concentration of PEG at the surface. One explanation for this is that these films were made by solvent casting. When casting from a solvent, the component that minimizes the surface free energy will migrate to the surface. This is because the coatings are dried in air. If they were dried in water, the situation would be different. Minimizing surface free energy is the mechanism by which surfactants work. In the case of solvent blends, low surface tension solvents, such as pentane or ethanol would preferentially be at the surface instead of high surface tension solvents such as DMAC. As the solvent concentration diminishes, the surface tension, or surface free energy of the dissolved polymers comes into play. PEG has a high surface tension of 43 dyne/cm.1 If the surface free energy of EVAL is less than this, then the EVAL will be preferentially at the surface. With more hydrophobic, low surface free energy polymers, such as Kynar, the driving force is even greater. So the underlying layer, dried in an air atmosphere may not have a surface rich in the hydrophilic additive. However, if a topmost layer is coated on top consisting of pure hydrophilic additive, PEG for example, or another very polar, hydrophilic material then the interface between the underlying layer and the topmost layer will be enriched with the hydrophilic additive. More specifically, the PEG of the underlying layer would favorable interact with the pure PEG of the topmost layer creating a very PEG rich interface. When this system is immersed in water, the topmost layer dissolves away revealing the surface of the underlying layer. This surface is PEG enriched and will remain so because it is now exposed to the very polar aqueous environment. The surface free energy of PEG exposed to air is 43 dyne/cm, but the surface free energy of the PEG/water interface is very low, less than 1 dyne/cm. In fact, if the PEG is not immobilized it dissolves away. The PEG will be immobilized in the surface of the underlying layer by entanglement. With mobile polymers above their Tg, such as PBMA, the PEG will work its way loose at some slow rate. With a higher Tg polymer such as EVAL or Butvar, the PEG will be much less mobile and will only leach very slowly, if at all. If the polymer has some crystallinity, which EVAL and Elasteon have, and portions of the PEG molecules at the surface are trapped in crystalline regions, then the PEG would be very long lived.

[2] olymers with a high degree of biocompatibility, a history of medical use, and that can also be cleared by the kidneys are appropriate for use in a topmost layer. The cutoff for renal clearance is known to be in the range of 20-50K depending on the size of the random coil in aqueous solution. Example polymers are dextran, hyaluronic acid, PEG, PEO, poly(vinyl alcohol), Pluronic surfactants, heparin, chitosan, sulfonated polystyrene, and HEMA.

An alternate coating configuration is also possible that is simpler, but less flexible in capabilities. In this scheme, there is still a hydrophilic, water soluble topmost layer.

A schematic is shown

below.



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Disclosure on a Heparin Coating PROJECT NO. TITLE for a Stand Using Freetmated Theysarin **BOOK NO.** Work continued from Page 5/4/02 Gospose 10 15 20 25 30 35 Work continued to Page SCIENTIFIC BINDERY PRODUCTIONS CHICAGO 60605 MADE IN USA DISCLOSED TO AND JINDERSTOOD BY 5/23/02 DATE 5/30/02 WITNESS

Miscibility of PEG 20K and Povidone 29K with EVAL and PBMA

Conducted by the DDT Group - Dept 1403

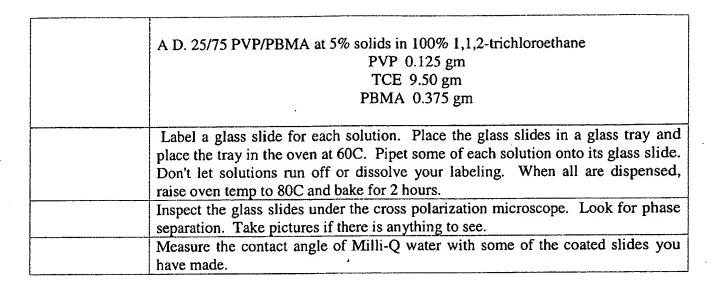
| R&D Technician | · . | |
|---------------------------|-----------------|------|
| | Bozena Maslanka | Date |
| R&D Engineer | | |
| | Stephen Pacetti | Date |

Miscibility of PEG 20K and Povidone 29K with EVAL and PBMA

Materials:

- PVP (Polyvinylpyrrolidone) Average Mw 29,000 100gm P/N 23425-7 lot#06306PO
- PEG (Polyethylene Glycol) Average Mw20,000 P/N 22568 lot#521420
- Fat free E151A EVAL
- DMAC RM2031749 lot#99232035
- PBMA lot#649000
- MeOH P/N 27,0474 lot#PO103620MO
- EtOH RM2034286 lot#99194913
- IPA P/N PX1838-1 lot#41355203
- Pipet
- glass slides
- vials 20cc
- iars
- polarization microscope
- oven
- Scale

| Test | Make a 10% stock solution of fat free E151A EVAL in DMAC. | | | | | | | | | |
|-----------------|--|---|--|--|--|--|--|--|--|--|
| Procedure: | Make a 10% stock solution of PBMA in DMAC. | | | | | | | | | |
| 1-44 | | | | | | | | | | |
| 1st set: | Make the following solutions. | | | | | | | | | |
| | All solutions will be 10 g total. | | | | | | | | | |
| | Use cleanest solvents we have. | | | | | | | | | |
| | A. 2/98 PEG /EVAL at 5% solids in DMAC | | | | | | | | | |
| • | B. 5/95 PEG /EVAL at 5% solids in DMAC | | | | | | | | | |
| | C. 10/90 PEG /EVAL at 5% solids in DMAC | | | | | | | | | |
| | D. 25/75 PEG /EVAL at 5% solids in DMAC | | | | | | | | | |
| | E. 2/98 PVP /EVAL at 5% solids in DMAC | | | | | | | | | |
| | F. 5/95 PVP /EVAL at 5% solids in DMAC | | | | | | | | | |
| | G. 10/90 PVP /EVAL at 5% solids in DMAC | | | | | | | | | |
| | H. 25/75 PVP /EVAL at 5% solids in DMAC | | | | | | | | | |
| | I. 2/98 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC | | | | | | | | | |
| | J. 5/95 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC | | | | | | | | | |
| | K. 10/90 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC | | | | | | | | | |
| | L. 25/75 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC | | | | | | | | | |
| | M. 100% EVAL at 5% solids in DMAC | | | | | | | | | |
| • | N. 100% PBMA at 5% solids in 50/50 MeOH/DMAC | | | | | | | | | |
| 2nd set: | Make the following solutions. | | | | | | | | | |
| (repeat) | All solutions will be 10 g total. | | | | | | | | | |
| | Use cleanest solvents we have. | | | | | | | | | |
| | A A. 2/98 PVP/PBMA at 5% solids in 100% 1,1,2-trichloroethane | | | | | | | | | |
| | PVP 0.01 gm | | | | | | | | | |
| | TCE 9.50 gm | | | | | | | | | |
| | PBMA 0.49 gm | | | | | | | | | |
| | A B. 5/98 PVP/PBMA at 5% solids in 100% 1,1,2-trichloroethane | | | | | | | | | |
| | PVP 0.025 gm | | | | | | | | | |
| | TCE 9.50 gm | | | | | | | | | |
| | PBMA 0.475 gm | | | | | | | | | |
| | A C. 10/90 PVP/PBMA at 5% solids in 100% 1,1,2-trichloroethane | | | | | | | | | |
| | PVP 0.05 gm | | | | | | | | | |
| | TCE 9.50 gm | | | | | | | | | |
| | PBMA 0.45 gm | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | · | | | | | | | | | |
| Cuidant Corners | Ation B Maslanka S Pacetti | - | | | | | | | | |



| Acceptance | Non-fouling surface of PEG and PVP molecules with polymers of interest. |
|------------|---|
| Criteria: | · |

Results: The EVAL and PBMA stock solution was mixed per MPI 2029382 Rev H

| - | Group | U | Solids Target | Solvent | Date mixed |
|---|------------|----------|---------------|----------|------------|
| | | Size (g) | (g) | DMAC (g) | |
| | EVAL Stock | 50.00 | 5.00 | 45.00 | 7/30/02 |
| | PBMA Stock | 50.00 | 5.00 | 45.00 | 8/01/02 |

Table 1

The following solution were mixed as listed below Table 2 & Table 3

| Solution formulation | Desired amount of coating solution (grams) | Desired % of solids | desire coating | Fraction of first polymer in solids | second polymer | Amount of first solid in grams | Name of first solid | | potymer in | Amount of Stock solution in grams | Name of 2nd polymer stock solution | Amount of DMAC to add to finished solution (grams) |
|-------------------------|--|---------------------------|----------------|--|-------------------|---|---------------------------|-------|------------|--|--|--|
| A | 10 | 5 | 0.5 | 0.02 | 0.98 | 0.01 | PEG | 0.490 | 0.1 | 4.90 | EVAL | 5.09 |
| 8 | 10 | 5 | 0.5 | 0.05 | 0.95 | 0.025 | PEG | 0.475 | 0.1 | 4.75 | EVAL | 5.23 |
| C | 10 | 5 | 0.5 | 0.1 | 0.90 | 0.05 | PEG | 0.450 | 0.1 | 4.50 | EVAL | 5.45 |
| D | 10 | 5 | 0.5 | 0.25 | 0.75 | 0.125 | PEG | 0.375 | 0.1 | 3.75 | EVAL | 6.13 |
| E | 10 | 5 | 0.5 | 0.05 | 0.95 | 0.03 | PVP | 0.475 | 0.1 | 4.75 | EVAL | 5.23 |
| F | 10 | 5 | 0.5 | 0.1 | 0.90 | 0.050 | PVP | 0.450 | 0.1 | 4.50 | EVAL | 5.45 |
| . G | 10 | 5 | 0.5 | 0.25 | 0.75 | 0.13 | PVP | 0.375 | 0.1 | 3.75 | EVAL | 6.13 |
| н | 10 | 5 | 0.5 | 0.25 | 0.75 | 0.125 | PVP | 0.375 | 0.1 | 3.75 | EVAL | 6.13 |
| м | 10 | 6 | 0.5 | 0 | 1.00 | 0.00 | EVAL | 0.500 | 0.1 | 5.00 | EVAL | 5.00 |

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| Solution formulation | | Desired % | | Fraction of first polymer in solids | % Of second polymer in solids | Amount of first solid in grams | first | How | polymer in stock | Amount of Stock | Name of 2nd polymer stock solution | Amount of DMAC to add to finished solution (grams) | Amount of IPA to add to finished solution (grams) |
|-------------------------|----|-----------|-----|---|-------------------------------|--------------------------------------|-------|-------|---------------------|--------------------|--|--|---|
| | | | | | | | Ī | | | | | | |
| | 10 | 5 | 0.5 | 0.02 | 0.98 | 0.01 | PVP | 0.490 | 0.1 | 4.90 | PBMA | 0.34 | 4.75 |
| J | 10 | 5 | 0.5 | 0.05 | 0.95 | 0.025 | PVP | 0.475 | 0.1 | 4.75 | PBMA | 0.48 | 4.75 |
| к | 10 | 5 | 0.5 | 0.1 | 0.90 | 0.05 | PVP | 0.450 | 0.1 | 4.50 | PBMA | 0.70 | 4.75 |
| L | 10 | 5 | 0.5 | 0.25 | 0.75 | 0.125 | PVP | 0.375 | 0.1 | 3.75 | PBMA | 1.38 | 4.75 |
| N | 10 | 5_ | 0.5 | .0 | 1.00 | 0 | РВМА | 0.500 | 0.1 | 5.00 | РВМА | 0.25 | 4.75 |

Table 3

When mixing formula I the solution became clumpy. The formula I was mixed again substituting MeOH for EtOH with same results. The formula was mixed once again substituting EtOH for IPA. With IPA the solution was clear and the remaining J through N was mixed with IPA.

When mixing solution A through D the PEG was added as the last component and during mixing of the solution it turned murky color. The formula A through D was mixed again but in different order. The PEG was mixed with DMAC until it dissolved and EVAL stock was added last.

Each glass slide was labeled and each of the solution was pipet out onto its glass slide. When all were dispensed, it was placed carefully into the oven and baked at 80 C for 2 hours.

Each glass slide was inspected for phase separation under the cross polarization microscope.

1st set of experiment:

| Solution formulation | Desired Solids in Stock Solution | Percentage of solids in solution | Visual observation | Microscope observation Crossed Polarizer |
|-------------------------|-------------------------------------|--|-----------------------|--|
| A-2 | PEG in EVAL | 2/98 | Little milky_ | Homogeneous |
| B-2 | PEG in EVAL | 5/95 | Little milky | Homogeneous, tiny crystals at edge |
| C-2_ | PEG in EVAL | 10/90 | Milky | Homogeneous in center, crystals at edge |
| D-2 | PEG in EVAL | 25/75 | Milky | Phase separation, many crystals |
| . Е | PVP in EVAL | 5/95 | Clear | Homogeneous |
| F | PVP in EVAL | 10/90 | Clear | Homogeneous |
| G | PVP in EVAL | 25/75 | Clear | Homogeneous |
| Н | PVP in EVAL | 25/75 | Clear | Homogeneous |
| 1 . | PVP in PBMA | 2/98 | Rough surface | Homogeneous |
| J | PVP in PBMA | 5/95 | Rough surface | Homogeneous |
| К | PVP in PBMA | 10/90 | Rough surface | Homogeneous |
| L | PVP in PBMA | 25/75 | Rough surface | Homogeneous |
| М | EVAL CONTROL | 100 | Clear | Homogeneous |
| N | PBMA CONTROL | 100 | Rough surface | Homogeneous |

Table 4

2nd set of experiment (repeat)

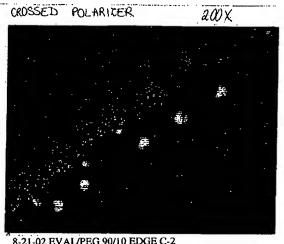
| Desired Solids in Stock Solution | Percentage of solids in solution | Visual observation | Microscope observation Crossed Polarizer |
|-------------------------------------|---|--|--|
| PVP in PBMA | 2/98 | Little milky | Homogeneous |
| PVP in PBMA | 5/95 | Little milky | Homogeneous |
| PVP in PBMA | 10/90 | Milky | Homogeneous |
| PVP in PBMA | 25/75 | Milky | Homogeneous |
| PEG in EVAL | 2/98 | Little milky | Homogeneous |
| PEG in EVAL | 5/95 | Little milky | Homogeneous tiny phase separation at edge |
| PEG in EVAL | 10/90 | Milky | Homogeneous in center, phase separation at edge |
| PEG in EVAL | <u>25</u> /75 | Milky | Phase separation |
| PVP in EVAL | 5/95 | Clear | Homogeneous |
| PVP in EVAL | 10/90 | Clear | Homogeneous |
| PVP in EVAL | 25/75 | Clear | Homogeneous |
| EVAL CONTROL | 100 | Clear | Homogeneous |
| · · · · · | PVP in PBMA PVP in EVAL PEG in EVAL PEG in EVAL PEG in EVAL PVP in EVAL PVP in EVAL PVP in EVAL | Desired Solids in Stock Solution of solids in solution PVP in PBMA 2/98 PVP in PBMA 5/95 PVP in PBMA 10/90 PVP in PBMA 25/75 PEG in EVAL 2/98 PEG in EVAL 5/95 PEG in EVAL 10/90 PEG in EVAL 5/95 PVP in EVAL 5/95 PVP in EVAL 10/90 PVP in EVAL 10/90 PVP in EVAL 25/75 | Desired Solids in Stock Solutionof solids in solutionVisual observationPVP in PBMA2/98Little milkyPVP in PBMA5/95Little milkyPVP in PBMA10/90MilkyPVP in PBMA25/75MilkyPEG in EVAL2/98Little milkyPEG in EVAL5/95Little milkyPEG in EVAL10/90MilkyPEG in EVAL25/75MilkyPVP in EVAL5/95ClearPVP in EVAL10/90ClearPVP in EVAL10/90ClearPVP in EVAL25/75Clear |

Table 5

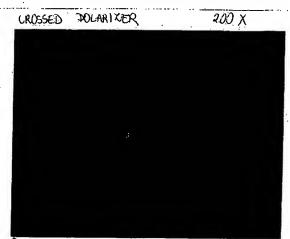
Two samples with phase separation were observed and photographed.

Sample C-2 with 10/90 PEG/EVAL the center was homogeneous with tiny phase separations at the edge as shown in Table 5.

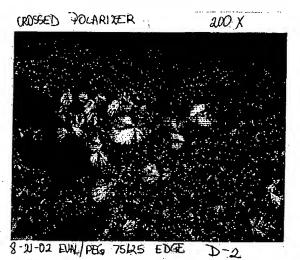
Sample D-2 with 25/75 PEG/EVAL the center was homogeneous with phase separations at the edge as shown in Table 6.



8-21-02 EVAL/PEG 90/10 EDGE C-2



8-21-02 EVAL/PEG 90/10 CENTER W/CONTAMINATION C-2 Table 5



CROSSED POLARIXER 200 X 75/25 CENTER 70-2

Table 6

Advancing and receding contact angle measurements were taken with a Rame-Hart Goniometer.

Advancing/Receding Contact Angle of DI on EVAL/PEG Blends, 1st Experiment

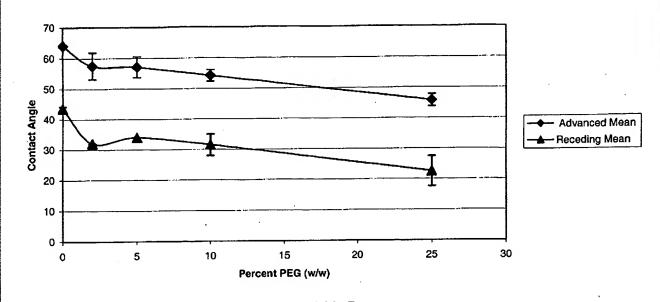


Table 7

Advancing/Receding Contact Angle of DI on EVAL/PVP Blends,
1st Experiment

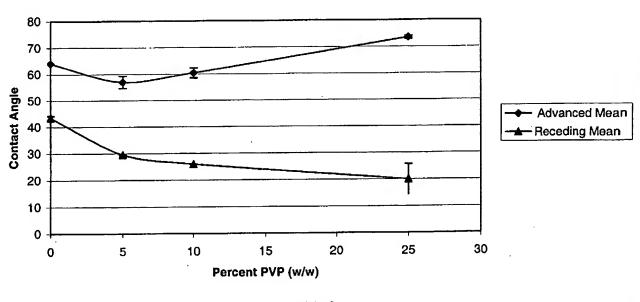
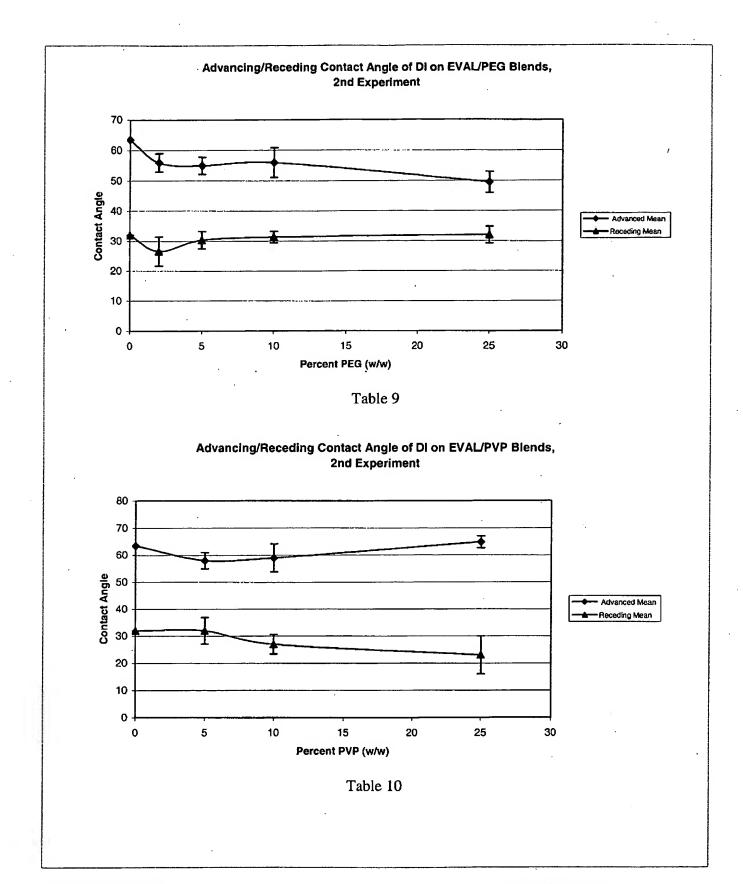
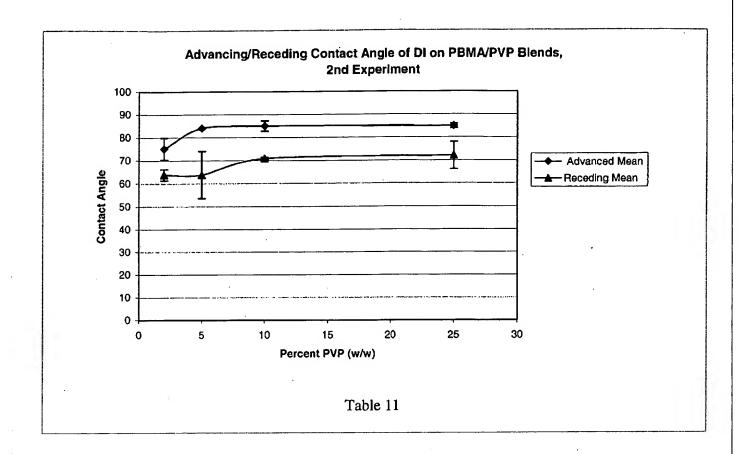


Table 8

A second set of slides were made to repeat contact angle measurements to ensure that it was contamination free.





Blends of PVP/EVAL showed slightly different behavior. Increasing levels of PVP actually increased the advancing contact angle. The receding angles were lower and PVP generally lowered the contact angle. In one case 25% PVP decreased the contact angle to 20 degrees, and in the second experiment, it decreased it to 22 degrees.

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